REMARKS

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27-37 will be pending in the present application upon entry of the amendment provided herein. Claims 1, 2, 5, 6, 10, 11, 14, 15, 19, 20 23, and 24 have been amended. New claims 28-37 have been added. Support for new claims 28-37 and the amendments to claims 1, 10, and 19 is found throughout the specification, e.g., at page 13, line 21 to page 14, line 16. Support for new claims 29-34 is also found in originally filed claims 6, 15, and 24. Support for new claims 35-37 is found at, e.g., page 3, lines 10-11. The specification has been amended to correct an informality with respect to the use of a trademarked term. Amendments have also made to correct typographical errors. No new matter is introduced by the amendments to the specification or claims. Amendments are made without disclaimer or prejudice.

Telephone Conference with Examiner

Applicant thanks the Examiner for the telephone conference on September 9, 2004, with Applicant's representative. The sole topic of discussion was clarification of a reference to joint inventors in the § 103 rejection in the Office Action dated May 14, 2004. The Examiner confirmed that the statement was an oversight and not relevant to the present application.

Specification

The Examiner has requested that the trademark CAMPTOSAR® be capitalized and accompanied by the generic terminology. The claims and specification have been amended to replace the term "CAMPTOSAR" with a generic term for the generic drug, "irinotecan." Also, the term "Camptosar" was inadvertently spelled "Captosar" in the paragraph beginning at page 6, line 6 and in the paragraph beginning at page 15, line 21, and as "Camtosar" in the paragraph beginning at page 3, line 8. The term was amended to "irinotecan."

Objection

The Office Action states that claim 10 is objected to because it contains the word "the" twice in line 3. Applicant has amended the claim to correct this informality.

35 U.S.C. § 112, Second Paragraph Rejections

Claims 1-6, 8-15, 17-24, 26, and 27 have been rejected for alleged indefiniteness related to the term "statistically significantly" (Office Action at page 3, fifth full paragraph). Applicant respectfully disagrees with the rejection.

Applicant asserts that the term "statistically significantly" is definite. The specification provides ample guidance regarding an acceptable method of determining statistical significance (i.e., an unpaired t-test), and a range of acceptable p values (i.e., from 0.08-0.0001) (e.g., application at page 13, line 21-page 14, line 16). Furthermore, since those in the art routinely use statistical methods, applicant believes that even without the guidance provided by the specification, one in the art would understand how to select a method of determining statistical significance. Thus, in view of the knowledge in the art and guidance provided by the specification, applicant does not believe that it is necessary to incorporate a specific statistical test or parameter into the claims.

Claims 2, 5, 6, 8, 9, and 28, 29, 30, and 35 depend from claim 1; claims 11, 14, 15, 17, 18, 31, 32, and 36 depend from claim 10; and claims 20, 23, 24, 26, 27, 33, 34, and 37 depend from claim 19. Therefore, all of the dependent claims incorporate the specific articulation of a statistical test and comply with the Examiner's apparent assertion that the information is necessary to define the metes and bounds of the claims.

In view of the above arguments, the rejection under 35 U.S.C. § 112, second paragraph is overcome for all of the pending claims. Accordingly, applicant respectfully requests reconsideration and withdrawal of the rejection.

35 U.S.C. § 112, First Paragraph (enablement) Rejections

Claims 1-6, 8-15, 17-24, 26, and 27 have been rejected for alleged lack of enablement. Claims 3, 4, 7, 12, 13, 16, 21, 22, and 25 have been canceled.

Applicant notes that the Examiner has asserted that the application is enabling for a method for statistically potentiating the activity of CAMPTOSAR® (irinotecan) using the conditions specified by the pending claims; but is not enabling for the method for statistically potentiating the activity of a prodrug (Office Action at page 5, first paragraph).

Applicant does not agree with this rejection. In particular, applicant asserts that the invention does not require "undue experimentation." However, to expedite prosecution, applicant has amended the independent claims (claims 1, 10, and 19) to indicate that the prodrug is an SN-38 prodrug. This amendment is commensurate with the Examiner's assertions regarding enabled material. In view of the amendments to the independent claims, applicant contends that the dependent claims are also enabled and respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102 (b) Rejections

Claims 1-5, 10-14, and 19-23 have been rejected for alleged anticipation by Koike et al. (Cancer Research, 1997, 57:5475-5479). Applicant respectfully disagrees with the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

All of the pending independent claims require co-administering an oligonucleotide with a prodrug. Applicant maintains that Koike et al. does not fulfill the requirements for anticipation of any of the pending claims. The Office Action states "Koike et al. teach a method for potentiating the activity of the prodrug CAMPTOSAR® (CPT-11) comprising administering an antisense oligonucleotide with the prodrug" (Office Action at page 10, fourth full paragraph, emphasis added). Applicant disagrees with this characterization of Koike et al. because Koike et al. did not use an oligonucleotide.

The present application provides a definition of an oligonucleotide:

> Oligonucleotides in antisense embodiments are preferably from about 13 to about 100 nucleotides in length, more preferably from about 15 to about 50, and most preferably from about 15-about 35. Oligonucleotides in non-antisense embodiments can be within these ranges, but can also preferably be from about 5 to about 15 nucleotides in length. (Specification at page 8, lines 23-27; emphasis added).

In contrast, Koike et al. constructed an antisense cMOAT expression vector using an 805 bp fragment "containing 77- bp of coding sequence and 35 bp of the 5' noncoding fragment sequence" (Koike et al., col. 2, last paragraph). Therefore, Koike et al. did not employ an oligonucleotide, and thus, cannot anticipate the pending claims.

Furthermore, Koike et al. uses a nucleic acid molecule that specifically targets a sequence while the claimed invention does not require the use of a specifically targeted oligonucleotide. Applicant also notes that the pending independent claim 1, and therefore dependent claims 2, 5, 6, and 9, specify that the oligonucleotide does not have two 5' or four 3' 2-O-methyl ribonucleosides. Koike et al. is silent on this issue and therefore does not provide this element of the claims.

Thus, as Koike et al. does not provide all elements of applicant's independent claims it cannot anticipate them. Nor can Koike et al. anticipate the pending dependent claims. Accordingly, in view of the arguments presented above, applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102.

35 U.S.C. § 103 Rejections

Claims 1-6, 8-15, 17-24, 26 and 27 have been rejected for alleged obviousness over Koike et al. (Cancer Research, 1997, 57:5475-5479) in view of U.S. Patent No. 5,801,154 (Baracchini et al.).

First, applicant notes that the Office Action states "[t]his application currently names joint inventors," and requests information under 37 C.F.R. 1.56 (Office Action at page 10, last paragraph bridging to page 11). However, the present application names a single inventor, not joint inventors. As discussed above, applicant's representative, Lisa Geller, spoke with the Examiner on September 9, 2004, to clarify this aspect of the Office Action. The Examiner indicated that the statement is not relevant to the present application and can be disregarded.

With respect to the rejection of the claims for obviousness over Koike et al. in view of Baracchini et al., applicant respectfully traverses the rejection.

Applicant submits that the combination of Koike et al. and Baracchini et al. does not establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify a reference or to combine reference teachings, there must be a reasonable expectation of success, and the references must teach or suggest all of the claim limitations (MPEP § 2143).

As discussed above, the pending claims are drawn to methods in which an oligonucleotide is co-administered with a prodrug. Koike et al. does not disclose the use of an oligonucleotide. Nor, with respect to claim 1 and the claims that depend from claim 1, does Koike et al. disclose the use of an oligonucleotide that does not have two 5' or four 3' 2-O-methyl ribonucleosides.

Baracchini et al. does not supply the deficiencies of Koike et al. Baracchini et al. discloses an antisense oligonucleotide targeted to a multidrug resistance protein, and the use of the oligonucleotide to reverse resistance to chemotherapeutic agents. Barrachini et al. does not teach a method for potentiating the activity of a prodrug by co-administering an oligonucleotide and a prodrug. In fact, Baracchini et al. does not even mention the use of a prodrug.

There is no reference whatsoever in Baracchini et al. to the improvement of the activity of a prodrug by administering an oligonucleotide. Thus, even if Baracchini could provide any of the deficiencies of Koike et al., there is no reason why one in the art would be motivated to combine Baracchini et al. with Koike et al. to make the present invention.

Applicant also notes that the Office Action asserts that one in the art "would have been motivated to modify the oligonucleotide of the instant invention since the metabolic stability of the oligonucleotide plays an important factor in statistically potentiating CPT-11 prodrug efficacy as evidenced by Agrawal et al. (International Journal of Oncology, 2001, Vol. 18:1061-1069)" (Office Action at page 13, first paragraph). Applicant notes that the present application was filed on November 8, 2000, and claims priority to November of 1999, long before Agrawal et al. was published. Thus, it would not have been possible for one in the art to use Agrawal et al., 2001, as reference to supply a motivation to make the present invention.

Since the cited references in combination do not provide all of the limitations of the pending claims, nor do they provide any motivation or suggestion make the claimed invention,

these references do not make obvious any of the independent claims (1, 10, and 19) or those dependent thereon.

In view of the foregoing, applicant respectfully requests that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

In view of the amendments to the claims and the arguments presented above, all of the claims are in condition for allowance, which action is respectfully requested.

This paper is accompanied by a Petition for Extension of Time and an Information Disclosure Statement/Form 1449 with authorization to charge the fees due.

Should any additional fees be deemed to be properly assessable in this application during its pendancy, or for the timely consideration of this Amendment, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. 08-0219, Order No. 111590-120.

If the Examiner believes that a telephone conference would expedite this matter, the Examiner is respectfully requested to telephone the applicant's undersigned attorney at (617) 526-6457.

Respectfully submitted,

WILMER CUTLER PICKERING HALE AND DORR LLP

Date: October 14, 2004

By: _____

Lisa N. Geller, Ph.D.
Registration No. 51,726

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000